GYNAECOLOGICAL CANCER

Viral gene therapy active in ovarian cancer

Advanced-stage ovarian cancers are typically sensitive to initial platinum-based therapy, but most recur and eventually develop platinum resistance. Effective therapies for platinum-resistant disease are an unmet need. New data suggest that ofranergene obadenovec (VB-111), a novel viral gene therapy, is active in this context.

VB-111 consists of an adenoviral vector carrying a *TNFR1–FAS* chimeric death receptor transgene with a modified pre-endothelin 1 promoter that is activated specifically in angiogenic endothelial cells. This agent is postulated to abrogate tumour angiogenesis through TNF-induced, TNFR1–FAS-mediated endothelial cell death. The associated tumour cell death and antigen release, as well as the immune adjuvant effect of the virus itself, might also result in enhanced antitumour immunity.

In a phase I/II trial, 21 women with ovarian cancer refractory or resistant to platinum-based chemotherapy received paclitaxel plus up to seven doses of VB-111. The phase II expansion cohort comprising 17 women who received the optimally tolerated 'therapeutic' dose of VB-111 and paclitaxel had a median overall survival of 16.6 months, compared with 5.8 months in those who received sub-therapeutic doses in phase I of the study ($P = 0.03$). Among the phase II cohort, 58% of evaluable patients had GCIG CA-125 responses, with a median duration of 10 months, and 73% had RECIST disease control (partial responses in 13%). Biopsy samples obtained from two patients after one or two doses of VB-111 had regions of tumour cell apoptosis as well as increased $CD8^+$ T cell and $CD4^+$ T cell infiltration compared with control specimens from untreated patients.

Treatment was well tolerated, with no dose-limiting toxicities. The most common adverse events (AEs) were fatigue (in 52% of patients), nausea (52%), fever (48%), anaemia (38%), diarrhoea (33%) and headache (29%). Serious AEs were reported in 29% of patients and grade ≥3 AEs in 43%.

These findings warrant larger-cohort randomized controlled trials of VB-111.

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ORIGINAL ARTICLE Arend, R. C. et al. *Gynecol. Oncol.* https://doi.org/10.1016/j.ygyno.2020.02.034 (2020)

COLORECTAL CANCER

Neoadjuvant immunotherapy shows promise

The successes achieved with immune-checkpoint inhibition (ICI) in patients with advanced-stage mismatch repair deficient (dMMR) colorectal cancers (CRCs) have largely not been replicated in those with mismatch repair proficient (pMMR) forms of CRC. Now data from the phase II NICHE study provide early evidence of safety and efficacy of neoadjuvant ICI in these subtypes.

After a preliminary safety run-in, in which three patients received the anti-PD-1 antibody nivolumab as monotherapy, a total of 37 patients (17 with pMMR CRC and 20 with dMMR CRC) received neoadjuvant therapy with one dose of the anti-CTLA4 antibody ipilimumab (1 mg/kg on day 1) plus two doses of nivolumab (3 mg/kg on days 1 and 14), with a predefined 6-week maximum time between consent and surgery. Safety and feasibility were the primary end points.

Four patients (10%) had grade ≥3 adverse events, including grade 3 rash or pruritus in two. All patients underwent radical resections as planned. Grade ≥3 surgery-related adverse events occurred in eight patients (20%), including wound and/or abdominal infections and anastomotic leaks (both in four patients (10%)).

Among 35 patients who received both agents and were eligible for efficacy evaluations (two patients with pMMR CRCs were deemed ineligible post-surgery), 100% of those with dMMR CRC and 27% with pMMR CRC had pathological responses. The majority of responders (19/20 with dMMR CRC and 3/15 with pMMR CRC) had major pathological responses, including 12 complete responses. Subsequent organoid-based investigations suggest that the lower response rates of patients with pMMR CRCs reflect a lack of highly immunogenic T cell antigens, as opposed to other tumour-intrinsic factors.

These data highlight the safety and preliminary efficacy of neoadjuvant ICI in patients with dMMR CRCs and potentially in a subset with pMMR CRCs. Data from larger cohorts of patients are eagerly awaited.

Peter Sidaway

ORIGINAL ARTICLE Chalabi, M. et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat. Med.* **26**, 566–576 (2020)

IMMUNOTHERAPY

Anti-CD22 CAR T cells in ALL

Anti-CD19 immunotherapies, including chimeric antigen receptor (CAR) T cells, have ushered in a new era of treatment for acute lymphoblastic leukaemia (ALL); however, resistance often occurs, typically via loss of CD19. Now, a phase I trial has provided new insights into the safety and efficacy of salvage therapy with anti-CD22 CAR T cells in this setting.

After fludarabine and cyclophosphamide conditioning therapy, 58 patients aged 4–31 years with $CD22^+$ B cell malignancies (56 with ALL) received various doses of anti-CD22 CAR T cells. Of these patients, 88% and 33% had received prior CD19-directed and CD22-directed therapies, respectively. The complete remission (CR) rate was 70%, and the median overall survival was 13.4 months. Among those with a CR, 87.5% had a minimal residual disease-negative response, and median relapse-free survival was 6 months. The response rate was unaffected by prior CD19-targeted therapy or haematopoietic stem cell transplantation, but prior receipt of CD22-targeted therapy was associated with inferior responses. At relapse, most patients had $CD22^{-/dim}$ disease.

Overall, 86% and 33% of patients had cytokine-release syndrome (CRS) and neurological toxicities, respectively, mostly of grade 1–2 (90% and 95%). However, two grade 5 adverse events occurred, one in association with CRS. Notably, haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)-like events occurred only in patients with CRS (38% of this group), with a delayed onset. Treatment of HLH/MAS was required in 14 of 19 patients, with 8 receiving the IL-1 receptor antagonist anakinra, and did not seem to impair CAR T cell activity.

In order to improve the feasibility and consistency of CAR T cell manufacturing, selection of $CD4^+$ T cells and $CD8^+$ T cells was performed for 32 patients (55%). This change increased the rate of HLH/MAS at the target dose of 1×10^6 cells/kg (from 17% to 71%; $P = 0.017$), despite a similar incidence and severity of CRS. This effect was mitigated to some extent by a dose reduction to 3×10^5 cells/kg (HLH/MAS rate of 44%), without compromising efficacy (CR rate 76%).

These findings reveal a perhaps unique toxicity profile of anti-CD22 CAR T cells. The efficacy data warrant further development of this treatment approach.

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